

## **REMARKS**

Claims 1, 3-7, 9-12 and 14-16 are pending in the case. Upon entry of the amendment, claims 12 and 14-16 will be pending in the case.

The Applicants have cancelled claims 1, 3-7 and 9-11 as set forth above, and submit that in view of the forgoing amendments and following arguments that the claims are now in a proper form for allowance.

### **I. Claim rejection for double patenting**

The Examiner has rejected claims 1-11 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of US Patent No. 6,753,423. The Applicants have canceled claims 1, 3-7, 9-11, the claims within claims 1-11 pending after the previous office action; therefore, the rejection is moot.

### **II. Claim rejections under 35 USC 112, paragraph 1**

The Examiner has rejected claims 1, 3-7 and 9-11 under 35 USC 112, paragraph 1 for failing to comply with the written description requirement. The Applicants have canceled claims 1, 3-7, 9-11; therefore, the rejection is moot.

### **III. Claim rejections under 35 USC 102(a) or (e)**

The Examiner has rejected claims 1, 3-7, 9-12 and 14-16 under 35 USC 102(a) or (e) as being anticipated by Dean et al. The Examiner states that Dean et al teach inhibiting expression of a nucleic acid comprising contacting cells or tissues with an antisense oligonucleotide, wherein the oligonucleotide comprises at least one lipophilic moiety, more specifically a cholesterol moiety. Dean et al. teach that oligonucleotides are contacted with animal cells either in vivo or in vitro, targeting nucleic acids in adult mice in vivo and resultant treatment of tumor. Dean et al. teach that the oligonucleotides can

be delivered to the liver. Dean et al teach delivery via colloidal dispersion systems with liposomes.

The Applicants submit that Dean does not teach a method of treatment of hepatic disease by administration of an oligonucleotide having at least two sterol moieties covalently bonded thereto. Although Dean et al teach that lipophilic moieties can be attached to oligonucleotides at a number of positions to enhance cellular uptake (col 8, ln 40-43), they do not teach enhanced hepatic uptake. In example 4, Dean et al teach the treatment of subcutaneous tumor, not hepatic disease or disorder, with oligonucleotides containing no sterol modifications. In the paragraph bridging pages 116 and 117 of the instant application it states that about 40% of an oligonucleotide without cholesterol modification is taken up by the liver, whereas almost all of an oligonucleotide with two cholesterol modifications is taken up by the liver. The substantial increase in delivery of the oligonucleotide to the liver would increase the activity of the oligonucleotide in the liver, providing a method for the treatment of hepatic disease or disorder. Dean et al teach that a hepatic catheter can be used to delivery oligonucleotide to the liver (col 15, ln 54-57). This physical method does not anticipate the use of chemical modifications of an oligonucleotide to target it to the liver. Colloidal dispersion systems and liposomes involve mixing oligonucleotides with lipophilic molecules, not covalent bondage of lipophilic groups to oligonucleotides. Therefore, it is not relevant to the currently pending claims. In view of the many distinctions indicated above, the Applicants submit that the currently pending claims, claims 12 and 14-16 are neither obvious nor anticipated by Dean et al.; therefore, the rejection is overcome.

#### **IV. Fees**

The Applicants hereby request that the Commissioner charge Deposit Account No. 500252 a total of \$635.00, the fee of \$60.00 for an extension in time of reply of one

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(1) month, a request for continued examination \$395.00, and \$180.00 information disclosure statement filed after issuance of the first office action, all small entity. It is believed that no further fee is due. However, if an additional fee is due, the Commissioner is hereby entitled to charge the fee to the Deposit Account listed above citing Reference No. ISIS-5028.

#### **IV. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, an early office action on the merits of the case is respectfully requested.

Date: November 30, 2005

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Respectfully submitted,



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